US006906094B2

(12) **United States Patent**
**Barvian et al.**

(10) **Patent No.: US 6,906,094 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **1,2,4-TRISUBSTITUTED BENZENES AS INHIBITORS OF 15-LIPOXYGENASE**

(75) Inventors: **Nicole Chantel Barvian**, Ann Arbor, MI (US); **Patrick Michael O'Brien**, Stockbridge, MI (US); **William Chester Patt**, Chelsea, MI (US); **Joseph Armand Picard**, Canton, MI (US); **Drago Robert Sliskovic**, Saline, MI (US)

(73) Assignee: **Warner-Lambert Company**, Morris Plains, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 135 days.

(21) Appl. No.: **10/362,104**

(22) PCT Filed: **May 8, 2001**

(86) PCT No.: **PCT/US01/14795**

§ 371 (c)(1),
(2), (4) Date: **Feb. 21, 2003**

(87) PCT Pub. No.: **WO01/96298**

PCT Pub. Date: **Dec. 20, 2001**

(65) **Prior Publication Data**

US 2004/0053983 A1 Mar. 18, 2004

**Related U.S. Application Data**

(60) Provisional application No. 60/211,498, filed on Jun. 14, 2000.

(51) **Int. Cl.**[7] ..... **A61K 31/404**; C07D 209/04

(52) **U.S. Cl.** ..... **514/415**; 548/490

(58) **Field of Search** ..... 548/490; 514/415

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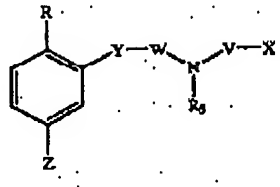
*Primary Examiner*—Golam M M Shameem
(74) *Attorney, Agent, or Firm*—Charles W. Ashbrook; Eric J. Baude; Claude F. Purchase, Jr.

(57) **ABSTRACT**

The present invention provides compounds of formula (I) wherein R, Z, Y, W, $R_5$, V, and X are as defined in the description, and pharmaceutically acceptable salts thereof, which are useful for the treatment of diseases responsive to the inhibition of the enzyme 15-lipoxygenase. Thus, the compounds of formula (I) and their pharmaceutically acceptable salts are useful for treating diseases with an inflammatory component, including atherosclerosis, diseases involving chemotaxis of monocytes, inflammation, stroke, coronary artery disease, asthma, arthritis, colorectal cancer, and psoriasis.

(I)




**16 Claims, No Drawings**


(12) **United States Patent**
**Tang et al.**

(10) **Patent No.: US 6,906,093 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **INDOLINONE COMBINATORIAL LIBRARIES AND RELATED PRODUCTS AND METHODS FOR THE TREATMENT OF DISEASE**

(75) Inventors: **Peng Cho Tang**, Moraga, CA (US); **Li Sun**, Foster City, CA (US); **Gerald McMahon**, San Francisco, CA (US); **Klaus Peter Hirth**, San Francisco, CA (US); **Laura Kay Shawver**, San Francisco, CA (US)

(73) Assignee: **Sugen, Inc.**, South San Francisco, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 25 days.

(21) Appl. No.: **09/897,755**

(22) Filed: **Jul. 3, 2001**

(65) **Prior Publication Data**

US 2002/0102608 A1 Aug. 1, 2002

**Related U.S. Application Data**

(63) Continuation of application No. 08/702,232, filed on Aug. 23, 1996, now abandoned, which is a continuation-in-part of application No. 08/655,255, filed on Jun. 5, 1996, now abandoned, which is a continuation-in-part of application No. 08/655,226, filed on Jun. 5, 1996, now Pat. No. 5,886,020, which is a continuation-in-part of application No. 08/655,223, filed on Jun. 5, 1996, now Pat. No. 5,792,783, which is a continuation-in-part of application No. 08/655,224, filed on Jun. 5, 1996, now Pat. No. 5,883,116, which is a continuation-in-part of application No. 08/659,191, filed on Jun. 5, 1996, now Pat. No. 5,883,113, which is a continuation-in-part of application No. 08/485,323, filed on Jun. 7, 1995, now Pat. No. 5,880,141.

(51) **Int. Cl.**[7] ..... **A61K 31/40**; C07D 209/02

(52) **U.S. Cl.** ..... **514/414**; 548/468

(58) **Field of Search** ..... 514/414; 548/468

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| EP | 0351213 | 1/1990 |
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*Assistant Examiner*—Kamal Saeed
(74) *Attorney, Agent, or Firm*—Beth A. Burrous; Foley & Lardner LLP

(57) **ABSTRACT**

The present invention relates to organic molecules capable of modulating tyrosine kinase signal transduction in order to regulate, modulate and/or inhibit abnormal cell proliferation.

**2 Claims, 56 Drawing Sheets**

US006906092B2

(12) **United States Patent**
**O'Brien et al.**

(10) **Patent No.: US 6,906,092 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **METHOD OF INHIBITING MATRIX METALLOPROTEINASES**

(75) Inventors: **Patrick Michael O'Brien**, Stockbridge, MI (US); **Joseph Armand Picard**, Canton, MI (US); **Drago Robert Sliskovic**, Saline, MI (US); **Andrew David White**, Pinckney, MI (US)

(73) Assignee: **Warner-Lambert Company**, Morris Plains, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 107 days.

(21) Appl. No.: **10/603,677**

(22) Filed: **Jun. 25, 2003**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

(62) Division of application No. 10/162,518, filed on Jun. 4, 2002, now Pat. No. 6,620,835, which is a division of application No. 09/254,384, filed as application No. PCT/US97/14859 on Aug. 22, 1997, now Pat. No. 6,624,177

(60) Provisional application No. 60/025,062, filed on Sep. 4, 1996, and provisional application No. 60/055,713, filed on Aug. 7, 1997.

(51) **Int. Cl.**[7] ..... **A61K 31/40**

(52) **U.S. Cl.** ..... **514/411**; 514/443; 514/444; 514/468; 514/601; 514/602; 514/603; 514/604; 514/605

(58) **Field of Search** ..... 514/411, 443, 514/444, 468, 601–605

(56) **References Cited**

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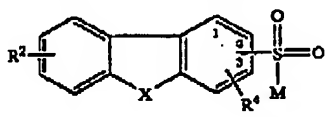
*Primary Examiner*—Dwayne Jones
(74) *Attorney, Agent, or Firm*—Pfizer Inc.; Charles W. Ashbrook; Claude F. Purchase, Jr.

(57) **ABSTRACT**

The present invention relates to a method of inhibiting matrix metalloproteinases using compounds that are dibenzofuran sulfonamide derivatives having the Formula I



More particularly, the present invention relates to a method of treating diseases in which matrix metalloproteinases are involved such as multiple sclerosis, atherosclerotic plaque rupture, restenosis, aortic aneurism, heart failure, periodontal disease, corneal ulceration, burns, decubital ulcers, chronic ulcers or wounds, cancer metastasis, tumor angiogenesis, arthritis, or other autoimmune or inflammatory diseases dependent upon tissue invasion by leukocytes.

**3 Claims, No Drawings**

US006906091B2

(12) **United States Patent**
**Camden**

(10) **Patent No.: US 6,906,091 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **METHOD OF CANCER TREATMENT**

(75) Inventor: **James Berger Camden**, West Chester, OH (US)

(73) Assignee: **UAF Technologies and Research, LLC**, Tucson, AZ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/198,334**

(22) Filed: **Jul. 18, 2002**

(65) **Prior Publication Data**

US 2003/0032664 A1 Feb. 13, 2003

**Related U.S. Application Data**

(63) Continuation of application No. 09/374,717, filed on Aug. 13, 1999, now Pat. No. 6,423,734.

(51) **Int. Cl.**[7] ..... **A61K 31/415**
(52) **U.S. Cl.** ..... **514/388**; 514/388
(58) **Field of Search** ..... 514/388

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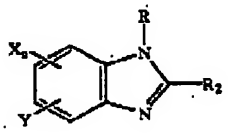
U.S. Appl. No. 09/552,825, filed Apr. 20, 2000, Camden.
U.S. Appl. No. 09/552,820, filed Apr. 20, 2000, Camden.
U.S. Appl. No. 09/560,059, filed Apr. 27, 2000, Camden.

(Continued)

*Primary Examiner*—Rebecca Cook
(74) *Attorney, Agent, or Firm*—Haynes and Boone, LLP

(57) **ABSTRACT**

Methods of treating and inhibiting cancer in animals by administering a therapeutically effective amount of a pharmaceutical composition having benzimidazole of the general formula:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, oxychloro, nitro, methyl or ethyl; and R is hydrogen, or an alkyl group of from 1 to 8 carbon atoms and $R_2$ is NHCOOR, wherein $R_1$ is aliphatic hydrocarbon of less than 7 carbon atoms, and preferably an alkyl group of less than 7 carbon atoms and pharmaceutically acceptable derivatives alone, or in combination, or in conduction with other therapeutic agents such as other cancer inhibiting compounds, and operative combinations thereof.

**10 Claims, No Drawings**

US006906090B1

(12) **United States Patent**
**Janakiraman**

(10) **Patent No.: US 6,906,090 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **COMPOSITIONS AND METHODS FOR TREATING MYCOBACTERIAL DISEASES**

(75) Inventor: **Ramachandran Janakiraman**, Bangalore (IN)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/284,516**

(22) PCT Filed: **Mar. 4, 1999**

(86) PCT No.: **PCT/SE99/00319**

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(2), (4) Date: **Apr. 14, 1999**

(87) PCT Pub. No.: **WO99/44608**

PCT Pub. Date: **Sep. 10, 1999**

(30) **Foreign Application Priority Data**

Mar. 6, 1998 (IN) ..... 464/MAS/98
Apr. 20, 1998 (SE) ..... 9801370

(51) **Int. Cl.**[7] ..... **A61K 31/415**; A61K 31/40; A61K 31/445; A61K 31/55

(52) **U.S. Cl.** ..... **514/387**; 514/418; 514/217.8; 514/217.9; 514/321; 514/322; 514/323; 540/575; 540/602; 540/603; 544/370; 544/373; 546/199; 546/201; 548/306.4; 548/486; 548/485

(58) **Field of Search** ..... 514/387, 418, 514/217.8, 217.9, 321, 322, 323; 540/575, 602, 603; 544/370, 373; 546/199, 201; 548/306.4, 486, 485

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*Primary Examiner*—D. Margaret Seaman
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

The invention provides the use of certain isatin and oxindole derivatives in the preparation of a medicament for use in the treatment of mycobacterial disease.

**7 Claims, No Drawings**

US006906089B2

(12) **United States Patent**
**Gaster et al.**

(10) **Patent No.: US 6,906,089 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **TRIARYLIMIDAZOLE DERIVATIVES AS CYTOKINE INHIBITORS**

(75) Inventors: **Laramie Mary Gaster**, Harlow (GB); **John David Harling**, Harlow (GB)

(73) Assignee: **SmithKline Beecham Corporation**, Philadelphia, PA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl No.: **10/239,815**

(22) PCT Filed: **Mar. 26, 2001**

(86) PCT No.: **PCT/GB01/01314**

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(2), (4) Date: **Jan. 21, 2003**

(87) PCT Pub. No.: **WO01/72737**

PCT Pub. Date: **Oct. 4, 2001**

(65) **Prior Publication Data**

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(30) **Foreign Application Priority Data**

Mar. 27, 2000 (GB) ..... 0007405

(51) **Int. Cl.**[7] ..... **A61K 31/443**; A61K 31/4436; A61K 31/4439; C07D 401/04; C07D 405/04

(52) **U.S. Cl.** ..... **514/341**; 514/341; 514/342; 514/343; 546/268.7; 546/269.4; 546/272.7; 546/280.4; 546/283.4

(58) **Field of Search** ..... 546/268.7, 269.4, 546/276.4, 272.7, 280.4, 283.4, 274.1; 514/341, 342, 343

(56) **References Cited**

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| JP | A11 180 958 | 7/1999 |
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| WO | WO9821957 | 5/1998 |
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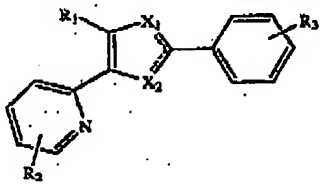
*Primary Examiner*—Cecilia Chang
*Assistant Examiner*—Janet L. Coppins
(74) *Attorney, Agent, or Firm*—Nora Steiu-Fernandez; Theodore R. Furman

(57) **ABSTRACT**

Compounds of formula (I) or a pharmaceutically acceptable salt thereof:

(I)



wherein $R_1$, $R_2$ and $R_3$ are various substituent groups; and one of $X_1$ and $X_2$ is N or CR", and the other is NR" or CHR" wherein R" is hydrogen, OH, $C_{1-6}$alkyl, or $C_{3-7}$cycloalkyl; or when one of $X_1$ and $X_2$ is N or CR" then the other may be S or O;

and their use as pharmaceuticals.

**9 Claims, No Drawings**


(12) **United States Patent**
**Holton et al.**

(10) **Patent No.: US 6,906,088 B2**
(45) **Date of Patent: *Jun. 14, 2005**

(54) **TAXANES HAVING A C10 CARBAMOYLOXY SUBSTITUENT**

(75) Inventors: **Robert A. Holton**, Tallahassee, FL (US); **Weishuo Fang**, Bejiang (CN)

(73) Assignee: **FSU Research Foundation, Inc.**, Tallahassee, FL (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 19 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/618,063**

(22) Filed: **Jul. 11, 2003**

(65) **Prior Publication Data**

US 2004/0034230 A1 Feb. 19, 2004

**Related U.S. Application Data**

(63) Continuation of application No. 09/775,852, filed on Feb. 2, 2001, now Pat. No. 6,596,737.
(60) Provisional application No. 60/179,793, filed on Feb. 2, 2000.

(51) **Int. Cl.**[7] ..... **A61K 31/4427**; A61K 31/381; A61K 31/341; A61K 31/337; C07D 305/14

(52) **U.S. Cl.** ..... **514/337**; 514/444; 514/471; 514/473; 514/449; 546/281.7; 549/60; 549/471; 549/510; 549/511

(58) **Field of Search** ..... 414/337; 514/444, 514/471, 473, 449; 546/281.7; 549/60, 471, 510, 511

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Ojima et al. "Synthesis and Biological Activity of Novel 3'–trifluoromethyl Taxoids" Bioorganic and Medicinal Chemistry Letters, vol. 7, No. 2 (1997) pp. 133–138.
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*Primary Examiner*—Ba K. Trinh
(74) *Attorney, Agent, or Firm*—Senniger Powers

(57) **ABSTRACT**

Taxanes having a carbamoyloxy substituent at C(10), a hydroxy substituent at C(7), and a range of C(2), C(9), C(14), and side chain substituents.

**32 Claims, No Drawings**


(12) **United States Patent**
**Van Der Schaaf et al.**

(10) **Patent No.: US 6,906,087 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **CRYSTALLINE FORMS OF VENLAFAXINE HYDROCHLORIDE**

(75) Inventors: **Paul Adriaan Van Der Schaaf**, Allschwil (CH); **Claudia Marcolli**, Zürich (CH); **Martin Szelagiewicz**, Münchenstein (CH); **Beat Freiermuth**, Buschwiller (FR)

(73) Assignee: **Ciba Specialty Chemicals Corpation**, Tarrytown, NY (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/130,042**

(22) PCT Filed: **Oct. 23, 2001**

(86) PCT No.: **PCT/EP01/12240**

§ 371 (c)(1),
(2), (4) Date: **Oct. 1, 2002**

(87) PCT Pub. No.: **WO02/36542**

PCT Pub. Date: **May 10, 2002**

(65) **Prior Publication Data**

US 2003/0105359 A1 Jun. 5, 2003

(30) **Foreign Application Priority Data**

Oct. 31, 2000 (EP) ..... 00811014

(51) **Int. Cl.**[7] ..... **A61K 31/135**

(52) **U.S. Cl.** ..... **514/336**; 564/336; 564/355; 564/424; 564/425; 564/360

(58) **Field of Search** ..... 514/646, 649; 564/336, 355, 424, 425, 360

(56) **References Cited**

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*Primary Examiner*—Samuel Barts
(74) *Attorney, Agent, or Firm*—Kevin T. Mansfield

(57) **ABSTRACT**

Crystalline forms of Venlafaxine hydrochloride were found, referred to hereinafter as polymorphic Forms A, B and D. Furthermore, the present invention is directed to processes for the preparation of these crystalline forms and pharmaceutical compositions comprising the crystalline forms.

**4 Claims, 6 Drawing Sheets**

US006906085B2

(12) **United States Patent**
**Castro Pineiro et al.**

(10) **Patent No.: US 6,906,085 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **TETRAHYDROPYRAN DERIVATIVES AS NEUROKININ RECEPTOR ANTAGONISTS**

(75) Inventors: **Jose Luis Castro Pineiro**, Bishops Stortford (GB); **Piotr Antoni Raubo**, Bishops Stortford (GB); **Christopher John Swain**, Duxford (GB)

(73) Assignee: **Merck Sharp & Dohme Ltd.**, Hoddesdon

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/466,700**

(22) PCT Filed: **Jan. 16, 2002**

(86) PCT No.: **PCT/GB02/00179**

§ 371 (c)(1),
(2), (4) Date: **Jul. 15, 2003**

(87) PCT Pub. No.: **WO02/057250**

PCT Pub. Date: **Jul. 25, 2002**

(65) **Prior Publication Data**

US 2004/0063974 A1 Apr. 1, 2004

(30) **Foreign Application Priority Data**

Jan. 17, 2001 (GB) ..... 0101246
Sep. 10, 2001 (GB) ..... 0121876

(51) **Int. Cl.**[7] ..... **A61K 31/35**; A61K 31/445; C07D 309/10; C07D 401/04; C07D 401/06

(52) **U.S. Cl.** ..... **514/326**; 514/382; 514/383; 514/384; 514/459; 514/460; 546/207; 549/416; 549/419; 548/252; 548/263.2; 548/268.8

(58) **Field of Search** ..... 546/207; 548/252, 548/263.2, 268.8; 514/382, 383, 384, 460, 459; 549/416, 419, 423

(56) **References Cited**

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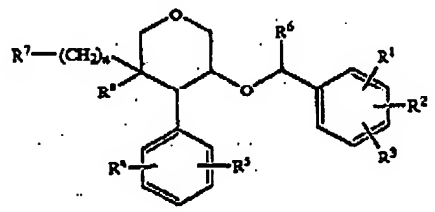
*Primary Examiner*—Bernard Dentz
(74) *Attorney, Agent, or Firm*—J. Eric Thies; Melvin Winokur

(57) **ABSTRACT**

The present invention relates compounds of the formula (I):

(I)



wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ represent a variety of substituents; and pharmaceutically acceptable salts thereof. The compounds are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.

**14 Claims, No Drawings**

US006906083B2

(12) **United States Patent**
**Iimura et al.**

(10) **Patent No.: US 6,906,083 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **4-SUBSTITUTED PIPERIDINE COMPOUND**

(75) Inventors: **Yoichi Iimura**, Ibaraki (JP); **Takashi Kosasa**, Ibaraki (JP)

(73) Assignee: **Eisai Co., Ltd.**, Tokyo (JP)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/296,379**

(22) PCT Filed: **Jun. 21, 2001**

(86) PCT No.: **PCT/JP01/05320**

§ 371 (c)(1),
(2), (4) Date: **Nov. 25, 2002**

(87) PCT Pub. No.: **WO01/98271**

PCT Pub. Date: **Dec. 27, 2001**

(65) **Prior Publication Data**

US 2003/0166925 A1 Sep. 4, 2003

(30) **Foreign Application Priority Data**

Jun. 21, 2000 (JP) ..... 2000-186085

(51) **Int. Cl.**[7] ..... **A61K 31/445**; C07D 211/06; C07D 211/32

(52) **U.S. Cl.** ..... **514/319**; 546/205; 546/206

(58) **Field of Search** ..... 514/319; 546/205, 546/206

(56) **References Cited**

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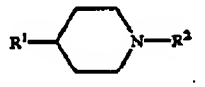
*Primary Examiner*—Celia Chang
(74) *Attorney, Agent, or Firm*—Birch, Stewart, Kolasch & Birch, LLP

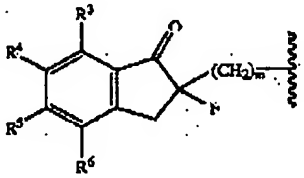
(57) **ABSTRACT**

The present invention provides a novel compound having a superior acetylcholinesterase inhibitory action. It provides a compound represented by the formula:

(I)



(In the formula, $R^1$ represents a group represented by the formula:



(wherein, $R^3$, $R^4$, $R^5$ and $R^6$ are the same as or different from each other and each represents a hydrogen atom, an optionally substituted $C_{1-6}$ alkoxy group and the like; and m represents an integer from 0 to 6) and the like; and $R^2$ represents a hydrogen atom, an optionally substituted $C_{1-6}$ alkyl group, an optionally substituted $C_{2-6}$ alkenyl group or an optionally substituted $C_{2-6}$ alkynyl group), a salt thereof or a hydrate of them.

**19 Claims, No Drawings**


(12) **United States Patent**
**DeNinno et al.**

(10) **Patent No.: US 6,906,082 B2**
(45) **Date of Patent: *Jun. 14, 2005**

(54) **4-CARBOXYAMINO-2-SUBSTITUTED-1,2,3,4-TETRAHYDROQUINOLINES**

(75) Inventors: **Michael P. DeNinno**, Gales Ferry, CT (US); **George T. Magnus-Aryitey**, Ledyard, CT (US); **Roger B. Ruggeri**, Waterford, CT (US); **Ronald T. Wester**, Ledyard, CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/607,640**

(22) Filed: **Jun. 27, 2003**

(65) **Prior Publication Data**

US 2004/0092550 A1 May 13, 2004

**Related U.S. Application Data**

(62) Division of application No. 09/685,380, filed on Oct. 10, 2000, now Pat. No. 6,586,448, which is a division of application No. 09/391,152, filed on Sep. 7, 1999, now Pat. No. 6,197,786.

(60) Provisional application No. 60/100,860, filed on Sep. 17, 1998.

(51) **Int. Cl.**[7] ..... **A61K 31/47**; C07D 215/38

(52) **U.S. Cl.** ..... **514/313**; 546/159

(58) **Field of Search** ..... 514/313; 546/159

(56) **References Cited**

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Chem. Abstract, vol. 116, 1992, 116:151569g.
Chem. Abstracts vol. 123, 1995, 123:55716b.

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*Primary Examiner*—D. Margaret Seaman
(74) *Attorney, Agent, or Firm*—Gregg C. Benson; Peter C. Richardson; A. Dean Olson

(57) **ABSTRACT**

Cholesteryl ster transfer protein inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein-cholesterol and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in some mammals, including humans.

**15 Claims, No Drawings**

US006906080B1

(12) **United States Patent**
**Barth et al.**

(10) **Patent No.: US 6,906,080 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **PYRAZOLECARBOXYLIC ACID TRICYCLIC DERIVATIVES, PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME**

(75) Inventors: **Francis Barth**, Saint-Georges-D'Orques (FR); **Christian Congy**, Saint-Gely-du-Fesc (FR); **Serge Martinez**, Montpellier (FR); **Murielle Rinaldi**, Saint-Georges-D'Orques (FR)

(73) Assignee: **Sanofi-Aventis**, Paris (FR)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/111,765**

(22) PCT Filed: **Nov. 2, 2000**

(86) PCT No.: **PCT/FR00/03049**

§ 371 (c)(1),
(2), (4) Date: **Jul. 30, 2002**

(87) PCT Pub. No.: **WO01/32663**

PCT Pub. Date: **May 10, 2001**

(30) **Foreign Application Priority Data**

Nov. 3, 1999 (FR) ..... 99 13846

(51) **Int. Cl.**[7] ..... **C07D 495/04**; A61K 31/4162; A61K 31/4439; A61K 31/438

(52) **U.S. Cl.** ..... **514/278**; 514/322; 514/406; 546/16; 546/199; 548/359.5

(58) **Field of Search** ..... 548/359.5; 514/406, 514/322, 278; 546/199, 16

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| EP | 0658546 | 12/1994 |
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| WO | WO 97/19063 | 5/1997 |

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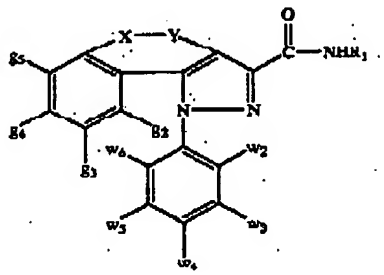
Fravolini, A. et al., Farmaco, Ed. Sci., vol. 33, No. 11, pp. 855–860 (1978).

*Primary Examiner*—Joseph K. McKane
*Assistant Examiner*—Rebecca Anderson
(74) *Attorney, Agent, or Firm*—Kelly Bender

(57) **ABSTRACT**

The subject of the invention is tricyclic derivatives of pyrazolecarboxylic acid of formula:

(I)



in which $R_1$ represents a $C_3$–$C_{15}$ carboxyl radical or an $NR_2R_3$ group. The invention also relates to the method for preparing the compounds of formula (I), pharmaceutical compositions containing them. The compounds of formula (I) are active on cannabinoid $CB_1$ receptors.

**11 Claims, No Drawings**

US006906079B2

(12) **United States Patent**
**Gutman et al.**

(10) **Patent No.: US 6,906,079 B2**
(45) **Date of Patent: *Jun. 14, 2005**

(54) **METHOD AND REAGENTS FOR N-ALKYLATING UREIDES**

(75) Inventors: **Daniela Gutman**, Rishon Lezion (IL); **Hershel Herzog**, Tarrytown, NY (US)

(73) Assignee: **Taro Pharmaceutical Industries Limited**, Haifa Bay (IL)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/687,712**

(22) Filed: **Oct. 17, 2003**

(65) **Prior Publication Data**

US 2004/0167358 A1 Aug. 26, 2004

**Related U.S. Application Data**

(63) Continuation of application No. 10/073,051, filed on Feb. 12, 2002, now Pat. No. 6,664,262, which is a continuation of application No. 09/609,902, filed on Jun. 30, 2000, now abandoned, which is a continuation of application No. 08/942,636, filed on Oct. 2, 1997, now Pat. No. 6,093,820.

(51) **Int. Cl.**[7] ..... **A61P 25/00; A61K 31/515**

(52) **U.S. Cl.** ..... **514/270**

(58) **Field of Search** ..... 514/270

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| EP | 726252 | 1/1996 |
| EP | 1 083 172 A1 | 3/2001 |
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| WO | W.O-02/07729 | 1/2002 |

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Salmon-Legagneur et al: "Sur les acides a-phenyl a-alcoyl (ou phenoalcoyl) glutariques"; Comptes Rendus de l'Academie des Sciences, (Mar. 3, 1952) p. 1060–1062.

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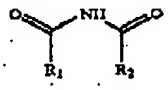
*Primary Examiner*—Bruck Kifle

(57) **ABSTRACT**

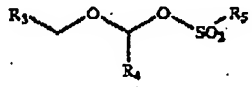
A method of N-alkoxyalkylating ureides according to the invention comprises reacting a ureide of structure I:

I



with an alkylating agent of structure III:

III



in the presence of a basic catalyst in an aprotic reaction medium. The ureide may be a 5,5-disubstituted barbituric acid, or it may be phenytoin, glutethimide, and ethosuximide. The alkylating agent is an ester of a sulfonic acid. The base may be a hydride or amine. A preferred process comprises N-alkoxyalkylating 5,5-diphenyl-barbituric acid with methoxymethyl methanesulfonate in the presence of di-isopropyl ethyl amine and isolating the resultant N,N'-bismethoxymethyl-5,5-diphenyl-barbituric acid. The invention also contemplates the novel compounds N-methoxymethyl-5,5-diphenylbarbituric acid, N-methoxymethyl ethosuximide, and N-methoxymethyl glutethimide, and a method comprising administering them to a patient.

**7 Claims, No Drawings**

US006906077B1

(12) **United States Patent**
**Pang**

(10) **Patent No.: US 6,906,077 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **USE OF NEUROTROPHIC FACTOR STIMULATORS FOR THE TREATMENT OF OPHTHALMIC NEURODEGENERATIVE DISEASES**

(75) Inventor: **Iok-hou Pang**, Grand Prairie, TX (US)

(73) Assignee: **Alcon Manufacturing, Ltd.**, Fort Worth, TX (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/856,987**

(22) PCT Filed: **Dec. 1, 1999**

(86) PCT No.: **PCT/US99/28385**

§ 371 (c)(1),
(2), (4) Date: **May 25, 2001**

(87) PCT Pub. No.: **WO00/32197**

PCT Pub. Date: **Jun. 8, 2000**

**Related U.S. Application Data**

(60) Provisional application No. 60/110,983, filed on Dec. 3, 1998.

(51) **Int. Cl.**[7] ..... **A61K 31/52**

(52) **U.S. Cl.** ..... **514/261**; 514/912

(58) **Field of Search** ..... 514/261, 912

(56) **References Cited**

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(74) *Attorney, Agent, or Firm*—Teresa J. Schultz

(57) **ABSTRACT**

Compositions and methods for the treatment of retina and optic nerve head neuropathy are disclosed. The compositions and methods are particularly directed to the use of neurotrophic factor stimulators, such as AIT-082 (neotrofin), in the treatment of glaucomatous neuropathy.

**9 Claims, No Drawings**


(12) **Unitcd States Patent**
**DeSimone et al.**

(10) **Patent No.: US 6,906,075 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **MELANIN CONCENTRATING HORMONE RECEPTOR LIGANDS: SUBSTITUTED BENZOIMIDAZOLE ANALOGUES**

(75) Inventors: **Robert W. DeSimone**, Durham, CT (US); **Cheryl Steenstra**, Meriden, CT (US); **Linda Gustavsan**, Guilford, CT (US); **Rajagopal Bakthavatchalam**, Madison, CT (US); **Alan Hutchison**, Madison, CT (US)

(73) Assignee: **Neurogen Corp.**, Branford, CT (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 58 days.

(21) Appl. No.: **10/339,111**

(22) Filed: **Jan. 9, 2003**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

(60) Provisional application No. 60/347,279, filed on Jan. 10, 2002.

(51) Int. Cl.[7] ..... **C07D 401/10**; A61K 31/445; A61K 31/495

(52) U.S. Cl. ..... **514/254.01**; 514/323; 514/399; 544/370; 546/201; 548/306.1

(58) Field of Search ..... 548/306.1; 514/399, 514/254.01, 323; 546/201; 544/370

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| WO | WO 00/59887 | 10/2000 |
| WO | WO 00/59905 | 10/2000 |
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| WO | WO 01/21577 | 3/2001 |
| WO | WO 01/82925 | 11/2001 |
| WO | WO 01/87834 | 11/2001 |
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*Primary Examiner*—Joseph K. McKane
*Assistant Examiner*—Golam M M Shameem
(74) *Attorney, Agent, or Firm*—Ann T. Kadlecek; Seth A. Fidel

(57) **ABSTRACT**

Melanin concentrating hormone receptor ligands (especially substituted benzoimidazole analogues), capable of modulating MCH receptor activity, are provided. Such ligands may be used to modulate MCH binding to MCH receptors in vivo or in vitro, and are particularly useful in the treatment of a variety of metabolic, feeding and sexual disorders in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for detecting MCH receptors (e.g., receptor localization studies).

**16 Claims, No Drawings**

US006906074B2

(12) **United States Patent**
**Ogino et al.**

(10) **Patent No.: US 6,906,074 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **2-PHENYLPIPERAZINE DERIVATIVES**

(75) Inventors: **Takashi Ogino**, Osaka (JP); **Yukari Konishi**, Hyogo (JP); **Kunihiko Higashimura**, Hyogo (JP); **Kazuhito Furukawa**, Hyogo (JP)

(73) Assignee: **Nippon Zoki Pharmaceutical Co., Ltd.**, Osaka (JP)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 131 days.

(21) Appl. No.: **10/370,918**

(22) Filed: **Feb. 20, 2003**

(65) **Prior Publication Data**

US 2003/0166616 A1 Sep. 4, 2003

(30) **Foreign Application Priority Data**

Feb. 22, 2002 (JP) ..... 2002-045562

(51) **Int. Cl.**[7] ..... **C07D 241/08**; C07D 403/06; A61K 31/50; A61K 31/501

(52) **U.S. Cl.** ..... **514/253.01**; 514/254.01; 514/254.05; 514/225.05; 514/255.03; 544/337; 544/360; 544/366; 544/372; 544/384; 544/389; 544/390; 544/391, 544/403

(58) **Field of Search** ..... 514/253.01, 254.01, 514/254.05, 255.02, 255.03; 544/337, 360, 366, 372, 384, 389, 390, 391, 403

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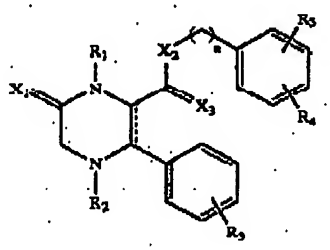
*Primary Examiner*—Thomas C. McKenzie
(74) *Attorney, Agent, or Firm*—Hollander Law Firm, P.L.C.

(57) **ABSTRACT**

A 2-phenylpiperazine derivative represented by the formula (I) or a pharmaceutically acceptable salt, hydrate, or complex thereof:

(I)



wherein each of $X_1$ and $X_3$ is oxygen or two hydrogen atoms, $X_2$ O, NH, $NCH_3$, or $CH_2$, n is an integer of 0 or 1, $R_1$ is hydrogen or lower alkyl and $R_2$ is hydrogen, cyano, tetrazolyl, aminotriazolyl , mesyl, t-butoxycarbonyl, or a lower alkyl which may be optionally substituted, $R_3$ is hydrogen, halogen, lower alkyl or lower alkoxy, each of $R_4$ and $R_5$ is hydrogen, lower alkoxy or trifluoromethyl, and a broken line indicates a single or double bond. The derivative may be used as a tachykinin antagonist in the treatment of diseases of the digestive system, nervous system and respiratory system, inflammation, allergy, carcinoid syndrome, chronic pain, headache, Crohn disease, depression and vomiting.

**18 Claims, No Drawings**

US006906073B2

(12) **United States Patent**
**Du Bois et al.**

(10) **Patent No.: US 6,906,073 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **PIPERAZINE CCR-3 RECEPTOR ANTAGONISTS**

(75) Inventors: **Daisy Joe Du Bois**, Palo Alto, CA (US); **Denis John Kertesz**, Mountain View, CA (US); **Eric Brian Sjogren**, Mountain View, CA (US); **David Bernard Smith**, San Mateo, CA (US); **Beihan Wang**, Santa Clara, CA (US)

(73) Assignee: **Roche Palo Alto LLC**, Palo Alto, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 49 days.

(21) Appl. No.: **10/307,159**

(22) Filed: **Nov. 29, 2002**

(65) **Prior Publication Data**

US 2003/0176441 A1 Sep. 18, 2003

**Related U.S. Application Data**

(60) Provisional application No. 60/334,655, filed on Nov. 30, 2001.

(51) Int. Cl.[7] ..... A61K 31/495; C07D 241/04

(52) U.S. Cl. ..... 514/252.13; 514/254.01; 514/254.1; 514/255.03; 544/372; 544/374; 544/393; 544/400

(58) Field of Search ..... 544/372, 374, 544/393, 400; 514/252.13, 254.01, 254.1, 255.03

(56) **References Cited**

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| WO | WO 00/35451 | 6/2000 | |
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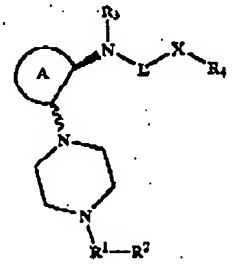
*Primary Examiner*—Richard L. Raymond
(74) *Attorney, Agent, or Firm*—Grant D. Green

(57) **ABSTRACT**

The invention provides compounds of Formula (I):

(I)



wherein: $R^1$–$R^4$, A, L, and X have any of the values defined in the specification that are CCR-3 receptor antagonists, pharmaceutical compositions containing them, methods for their use, and methods and intermediates useful for preparing them.

**20 Claims, No Drawings**

US006906072B1

(12) **United States Patent**
**Yamamoto et al.**

(10) **Patent No.: US 6,906,072 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **PIPERAZINE COMPOUND AND PHARMACEUTICAL COMPOSITION CONTAINING THE COMPOUND**

(75) Inventors: **Noboru Yamamoto**, Ibaraki (JP); **Yuichi Suzuki**, Ibaraki (JP); **Manami Kimura**, Chiba (JP); **Tetsuhiro Nikkome**, Ibaraki (JP); **Yoichi Iimura**, Ibaraki (JP); **Tetsuyuki Teramoto**, Brookline, MA (US); **Yoshihisa Kaneda**, Ibaraki (JP); **Toshihiko Kaneko**, Ibaraki (JP); **Nobuyuki Kurusu**, Ibaraki (JP); **Daisuke Shinmyo**, Ibaraki (JP); **Yukie Yoshikawa**, Ibaraki (JP); **Shinji Hatakeyama**, Ibaraki (JP)

(73) Assignee: **Eisai Co., Ltd.**, Tokyo (JP)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/169,837**

(22) PCT Filed: **Jan. 18, 2001**

(86) PCT No.: **PCT/JP01/00288**

§ 371 (c)(1),
(2), (4) Date: **Jul. 10, 2002**

(87) PCT Pub. No.: **WO01/53258**

PCT Pub. Date: **Jul. 26, 2001**

(30) **Foreign Application Priority Data**

Jan. 20, 2000 (JP) ..... 2000-012176

(51) **Int. Cl.**[7] ..... **C07D 409/06**; A61K 31/496; A61P 25/00; A61P 25/04

(52) **U.S. Cl.** ..... **514/252.13**; 544/379

(58) **Field of Search** ..... 514/252.12, 252.13, 514/253.01, 253.02, 253.11, 254.02, 254.03, 254.04, 254.06, 254.07, 254.11, 255, 2.3; 544/359, 360, 363, 364, 367, 368, 369, 366, 370, 37, 376, 377, 379, 391, 392, 402

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| 5,420,131 | A | 5/1995 | Carceller et al. | 514/253 |
| 6,117,875 | A | 9/2000 | Shimazaki et al. | 514/253.01 |
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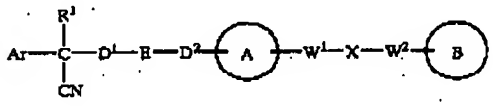
*Primary Examiner*—Thomas McKenzie
(74) *Attorney, Agent, or Firm*—Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

The present invention provides a novel compound having a superior calcium antagonism, in particular, a neuron-selective calcium antagonism. Namely, it provides a compound represented by the following formula, a salt thereof or a hydrate of them.

(I)



In the formula, Ar indicates an optionally substituted 5- to 14-membered aromatic ring etc.; the ring A indicates any one ring selected from a piperazine, a homopiperazine, a piperidine and the like; the ring B indicates an optionally substituted $C_{3-14}$ on hydrocarbon ring etc.; E indicates a single bond, a group represented by the formula —CO—, etc.; X indicates a single bond, an oxygen atom etc.; $R^1$ indicates a hydrogen atom, a halogen atom, a hydroxyl group etc.; and $D^1$, $D^2$, $W^1$ and $W^2$ are the same as or different from each other and each represents a single bond or an optionally substituted $C_{1-6}$ alkylene chain.

**16 Claims, 3 Drawing Sheets**

US006906070B2

(12) **United States Patent**
**Lam et al.**

(10) **Patent No.: US 6,906,070 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **GUANIDINE MIMICS AS FACTOR XA INHIBITORS**

(75) Inventors: **Patrick Y. Lam**, Chadds Ford, PA (US); **Charles G. Clark**, Cherry Hill, NJ (US); **Celia Dominguez**, Westlake, CA (US); **John M. Fevig**, Lincoln University, PA (US); **Qi Han**, Wilmington, DE (US); **Renhua Li**, Wilmington, DE (US); **Donald J. P. Pinto**, Kennett Square, PA (US); **James R. Pruitt**, Landenberg, PA (US); **Mimi L. Quan**, Newark, DE (US)

(73) Assignee: **Bristol-Myers Squibb Pharma Company**, Princeton, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 677 days.

(21) Appl. No.: **09/924,381**

(22) Filed: **Aug. 8, 2001**

(65) **Prior Publication Data**

US 2002/0025963 A1 Feb. 28, 2002

**Related U.S. Application Data**

(62) Division of application No. 09/099,358, filed on Jun. 18, 1998, now Pat. No. 6,339,099.
(60) Provisional application No. 60/050,265, filed on Jun. 20, 1997.

(51) **Int. Cl.**[7] ..... **A61K 31/4725**; C07D 401/04

(52) **U.S. Cl.** ..... **514/248**; 514/249; 514/266.2; 514/266.23; 514/300; 514/310; 514/313; 514/314; 514/373; 514/379; 514/395; 514/405; 514/406; 544/237; 544/258; 544/259; 544/260; 544/284; 544/293; 546/122; 546/143; 546/159; 548/207; 548/241; 548/304.7; 548/306.1; 548/362.1; 548/364.1; 548/364.4

(58) **Field of Search** ..... 514/266.2, 266.23, 514/266.4, 310, 313, 314, 379, 394, 395, 405, 406; 544/284, 293; 546/143, 159; 548/241, 304.7, 306.1, 356.1, 362.1, 364.1, 364.4

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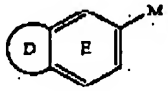
*Primary Examiner*—Richard L. Raymond
(74) *Attorney, Agent, or Firm*—David H. Vance; Jing S. Belfield

(57) **ABSTRACT**

The present application describes nitrogen containing heteroaromatics and derivatives thereof of formula I:

I




or pharmaceutically acceptable salt forms thereof, wherein rings D-E represent guanidine mimics, which are useful as inhibitors of factor Xa.

**16 Claims, No Drawings**


(12) **United States Patent**
**Li et al.**

(10) **Patent No.: US 6,906,069 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **LXR MODULATORS**

(75) Inventors: **Leping Li**, Burlingame, CA (US); **Julio C. Medina**, San Carlos, CA (US); **Bei Shan**, Redwood City, CA (US)

(73) Assignee: **Amgen Inc.**, Thousand Oaks, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/479,315**

(22) Filed: **Jan. 6, 2000**

**Related U.S. Application Data**

(60) Provisional application No. 60/115,292, filed on Jan. 8, 1999.

(51) **Int. Cl.**[7] ..... **A01N 43/58**

(52) **U.S. Cl.** ..... **514/247**; 514/461; 514/277; 514/438; 514/439

(58) **Field of Search** ..... 546/283.4; 514/336

(56) **References Cited**

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*Primary Examiner*—James O. Wilson
*Assistant Examiner*—Jason H. Johnsen
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

(57) **ABSTRACT**

The invention provides compounds, compositions and methods for modulating the effects of LXRα in a cell. The compounds and compositions are useful both as diagnostic indicators of LXRα function and as pharmacologically active agents. The compounds and compositions find particular use in the treatment of disease states associated with cholesterol metabolism, particularly atherosclerosis and hypercholesterolemia.

**24 Claims, No Drawings**

US006906068B1

(12) **United States Patent**
**South et al.**

(10) **Patent No.: US 6,906,068 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL 1,2,4 - TRIAZINONES USEFUL AS ANTICOAGULANTS**

(75) Inventors: **Michael S. South**, St. Louis, MO (US); **Ashton T. Hamme, II**, St. Louis, MO (US); **William L. Neumann**, St. Louis, MO (US); **Darin E. Jones**, Ballwin, MO (US)

(73) Assignee: **Pharmacia Corporation**, St. Louis, MO (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/009,447**

(22) PCT Filed: **May 17, 2000**

(86) PCT No.: **PCT/US00/09806**

§ 371 (c)(1),
(2), (4) Date: **Apr. 3, 2002**

(87) PCT Pub. No.: **WO00/69832**

PCT Pub. Date: **Nov. 23, 2000**

**Related U.S. Application Data**

(60) Provisional application No. 60/134,794, filed on May 19, 1999.

(51) **Int. Cl.**[7] ..... **C07D 253/065**; C07D 239/02; A61K 31/53; A61K 31/513; A61P 7/02

(52) **U.S. Cl.** ..... **514/242**; 514/269; 514/231.5; 544/182; 544/317; 544/111

(58) **Field of Search** ..... 544/182; 514/242

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*Primary Examiner*—Venkataraman Balasubramanian

(57) **ABSTRACT**

The invention relates to substituted polycyclic aryl and heteroaryl pyrimidinone compounds useful as inhibitors of serine proteases of the coagulation cascade and compounds, compositions and methods for anticoagulant therapy for the treatment and prevention of a variety of thrombotic conditions including coronary artery and cerebrovascular diseases.

**15 Claims, No Drawings**

US006906067B2

(12) **United States Patent**
**Moriarty et al.**

(10) **Patent No.: US 6,906,067 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **N-HETEROCYCLIC INHIBITORS OF TNF-α EXPRESSION**

(75) Inventors: **Kevin Joseph Moriarty**, Norristown, PA (US); **Yvonne Shimshock**, Hillsborough, NJ (US); **Gulzar Ahmed**, Yardley, PA (US); **Junjun Wu**, Malden, MA (US); **James Wen**, Dayton, NJ (US); **Wei Li**, Acton, MA (US); **Shawn David Erickson**, Leonia, NJ (US); **Jeffrey John Letourneau**, East Windsor, NJ (US); **Edward McDonald**, Banstead (GB); **Katerina Leftheris**, Skillman, NJ (US); **Stephen T. Wrobleski**, Whitehouse Station, NJ (US); **Zahid Hussain**, Monmouth Junction, NJ (US); **Ian Henderson**, Hopewell, NJ (US); **Axel Metzger**, East Windsor, NJ (US); **John J. Baldwin**, Gwynedd Valley, PA (US); **Alaric J. Dyckman**, Lawrenceville, NJ (US)

(73) Assignees: **Bristol-Myers Squibb Company**, Princeton, NJ (US); **Pharmaceopeia, Inc.**, Cranbury, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/891,750**

(22) Filed: **Jun. 26, 2001**

(65) **Prior Publication Data**

US 2002/0137747 A1 Sep. 26, 2002

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/747,195, filed on Dec. 22, 2000.

(60) Provisional application No. 60/173,227, filed on Dec. 28, 1999.

(51) **Int. Cl.**[7] ..... **C07D 251/40**; C07D 251/48; C07D 251/52; A61K 31/53; A61P 35/00

(52) **U.S. Cl.** ..... **514/241**; 514/197; 544/198; 544/208; 544/209; 544/213; 544/217; 544/218

(58) **Field of Search** ..... 544/197, 198, 544/208, 209, 213, 217, 218, 194; 514/241

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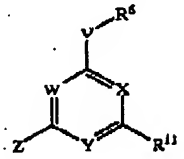
*Primary Examiner*—Venkataraman Balasubramanian
(74) *Attorney, Agent, or Firm*—Joseph C. Wang; Anastasia P. Winslow

(57) **ABSTRACT**

N-heterocyclic compounds that block cytokine production via inhibition of p38 kinase are disclosed. In one embodiment, compounds of the present invention are represented by Formula I:

I



Methods of production, pharmaceutical compositions and methods of treating conditions associated with inappropriate p38 kinase activity or TNF-α expression utilizing compounds of the present invention are also disclosed.

**20 Claims, No Drawings**

US006906066B2

(12) **United States Patent**
**Ko et al.**

(10) **Patent No.: US 6,906,066 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **N-UREIDOALKYL-PIPERIDINES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY**

(75) Inventors: **Soo S. Ko**, Hockessin, DE (US); **George V. Delucca**, Pennington, NJ (US); **John V. Duncia**, Newtown, PA (US); **Joseph B. Santella, III**, Springfield, PA (US); **Dean A. Wacker**, Yardley, PA (US); **Paul S. Watson**, Carrboro, NC (US); **Jeffrey G. Varnes**, Newtown, PA (US); **Wenqing Yao**, Kennett Square, PA (US)

(73) Assignee: **Bristol-Myers Squibb Pharma Company**, Princeton, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 43 days.

(21) Appl. No.: **10/465,191**

(22) Filed: **Jun. 19, 2003**

(65) **Prior Publication Data**

US 2004/0058960 A1 Mar. 25, 2004

**Related U.S. Application Data**

(60) Division of application No. 09/598,821, filed on Jun. 21, 2000, now Pat. No. 6,605,623, which is a continuation-in-part of application No. 09/465,286, filed on Dec. 17, 1999, now abandoned.

(60) Provisional application No. 60/112,717, filed on Dec. 18, 1998, and provisional application No. 60/161,243, filed on Oct. 22, 1999.

(51) **Int. Cl.**[7] ..... **C07D 211/08**; A61K 31/44

(52) **U.S. Cl.** ..... **514/237.2**; 514/326; 514/331; 544/129; 546/209; 546/210; 546/231

(58) **Field of Search** ..... 546/209, 210, 546/231; 544/129; 514/237.2, 326, 331

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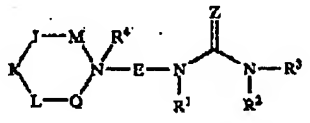
*Primary Examiner*—Deepak Rao
(74) *Attorney, Agent, or Firm*—Mary VanAllen

(57) **ABSTRACT**

The present application describes modulators of CCR3 of formula (I):

(I)



or pharmaceutically acceptable salt forms thereof, useful for the prevention of asthma and other allergic diseases.

**31 Claims, No Drawings**

US006906065B2

(12) **United States Patent**
**Thomas**

(10) **Patent No.: US 6,906,065 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **4-AMINO-5-CYANO-2-ANILINO-PYRIMIDINE DERIVATIVES AND THEIR USE AS INHIBITORS OF CELL-CYCLE KINASES**

(75) Inventor: **Andrew Peter Thomas**, Macclesfield (GB)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 20 days.

(21) Appl. No.: **10/239,790**

(22) PCT Filed: **Mar. 23, 2001**

(86) PCT No.: **PCT/GB01/01264**

§ 371 (c)(1),
(2), (4) Date: **Sep. 25, 2002**

(87) PCT Pub. No.: **WO01/72717**

PCT Pub. Date: **Oct. 4, 2001**

(65) **Prior Publication Data**

US 2003/0087923 A1 May 8, 2003

(30) **Foreign Application Priority Data**

Mar. 28, 2000 (GB) ..... 0007371

(51) **Int. Cl.**[7] ..... **C07D 239/48**; A61K 31/505

(52) **U.S. Cl.** ..... **514/235.8**; 514/275; 544/122; 544/323; 544/324

(58) **Field of Search** ..... 544/122, 323, 544/324; 514/235.8, 275

(56) **References Cited**

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| WO | 92/20642 | | 11/1992 |
| WO | 95/09847 | | 4/1995 |
| WO | 95/09851 | | 4/1995 |
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| WO | 95/09853 | | 4/1995 |
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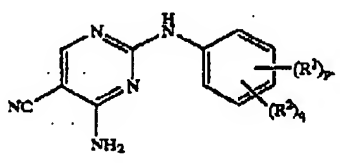
*Primary Examiner*—Deepak Rao
(74) *Attorney, Agent, or Firm*—Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

Compounds of formula (I) wherein: $R^1$ is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, $C_{1-6}$alkyl, $C_{2-6}$alkenyl or $C_{2-6}$alkynyl; p is 0–4; wherein the values of $R^1$ may be the same or different; $R^2$ is sulphamoyl or a group B-E- ; wherein B is optionally substituted as defined within and is selected from $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{3-8}$cycloalkyl, $C_{1-6}$alkyl, phenyl, a heterocyclic group, phenyl$C_{1-6}$alkyl or (heterocyclic group)$C_{1-6}$alkyl; E is C(O)—, $N(R^a)C(O)$—, —$C(O)N(R^a)$—, —S(O),—, —$SO_2N(R^a)$— or —$N(R^a)SO_2$—; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl optionally substituted as defined within and r is 1–2; q is 0–2; wherein the values of $R^2$ may be the same or different; and wherein p+q=1–5; or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof are described. Processes for their manufacture and their use as inhibitors of cell cycle kinases, particularly CDK2, CDK4 and/or CDK6 are also described

(I)



11 Claims, No Drawings

US006906063B2

(12) **United States Patent**
**Scarborough et al.**

(10) **Patent No.: US 6,906,063 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **PLATELET ADP RECEPTOR INHIBITORS**

(75) Inventors: **Robert M. Scarborough**, Half Moon Bay, CA (US); **Wolin Huang**, Foster City, CA (US); **Charles K. Marlowe**, Redwood City, CA (US); **Kim A. Kane-MaGuire**, Belmont, CA (US)

(73) Assignee: **Portola Pharmaceuticals, Inc.**, So. San Francisco, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 318 days.

(21) Appl. No.: **09/920,325**

(22) Filed: **Aug. 2, 2001**

(65) **Prior Publication Data**

US 2002/0077486 A1 Jun. 20, 2002

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/775,812, filed on Feb. 5, 2001, now abandoned, and a continuation-in-part of application No. PCT/US01/03585, filed on Feb. 5, 2001.

(60) Provisional application No. 60/230,447, filed on Sep. 6, 2000, provisional application No. 60/202,072, filed on May 5, 2000, and provisional application No. 60/180,208, filed on Feb. 4, 2000.

(51) **Int. Cl.**[7] ..... **C07D 417/12**; C07D 411/12; C07D 417/14; C07D 401/04; A61K 31/40

(52) **U.S. Cl.** ..... **514/222.8**; 514/231.5; 514/292; 514/293; 514/309; 544/9; 544/125; 544/126; 546/81; 546/82; 546/83; 546/141; 546/142

(58) **Field of Search** ..... 514/222.8, 231.5, 514/292, 293, 309; 544/9, 125, 126; 546/81, 82, 83, 141, 142

(56) **References Cited**

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*Primary Examiner*—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

(57) **ABSTRACT**

Novel compounds of formulae (I) to (VIII), which more particularly include sulfonylurea derivatives, sulfonylthiourea derivatives, sulfonylguanidine derivatives, sulfonylcyanoguanidine derivatives, thioacylsulfonamide derivatives, and acylsulfonamide derivatives which are effective platelet ADP receptor inhibitors. These derivatives may be used in various pharmaceutical compositions, and are particularly effective for the prevention and/or treatment of cardiovascular diseases, particularly those diseases related to thrombosis. The invention also relates to a method for preventing or treating thrombosis in a mammal comprising the step of administering a therapeutically effective amount of a compound of formulae (I) to (VIII), or a pharmaceutically acceptable salt thereof.

**8 Claims, No Drawings**


(12) **United States Patent**
**Chhabada et al.**

(10) **Patent No.: US 6,906,062 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **CRYSTALLINE FORM I OF 2-METHYL-4-(4-MENTHYL-1-PIPERAZINYL) 10H THIENO [2,3-B][1,5]BENZODIAZEPINE**

(75) Inventors: **Vijay Chhangamal Chhabada**, Baroda (IN); **Rajeev Budhdev Rehani**, Baroda (IN); **Rajamamannar Thennati**, Baroda (IN)

(73) Assignee: **Sun Pharmaceutical Industries Limited**, Maharashtra (IN)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/326,397**

(22) Filed: **Dec. 23, 2002**

(65) **Prior Publication Data**

US 2003/0125322 A1 Jul. 3, 2003

(30) **Foreign Application Priority Data**

Dec. 24, 2001 (IN) ..... 1211/2001

(51) **Int. Cl.**[7] ..... **A61P 25/18**; A61K 31/55; C07D 495/04

(52) **U.S. Cl.** ..... **514/220**; 540/557

(58) **Field of Search** ..... 514/220; 540/557

(56) **References Cited**

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*Primary Examiner*—Brenda Coleman
(74) *Attorney, Agent, or Firm*—Westerman, Hattori Daniels & Adrian LLP

(57) **ABSTRACT**

Crystalline Form I of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine characterised by x-ray powder diffraction peaks at approximately 9.94, 8.53, 8.19, 6.86, 6.35, 5.47, 4.83, 4.71, 4.53, 4.22, 4.08, 3.82, 3.75, 3.69, 3.50, 3.34, 3.11, 2.94, 2.82, 2.76, 2.59, 2.34, 2.03, 1.92 d (interplanar spacing) values; infrared absorbance bands at approximately 1456, 1365, 905, 757, 662 & 604 $cm^{-3}$ and having stable colour at ambient conditions of storage; and the process of its preparation comprising at least two repetitive steps of crystallization from one or more organic solvent by dissolving 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine in said solvent and allowing crystallization to occur; wherein in at least one step the solution is purified by treating with a solid adsorbent material and filtering; and wherein in the last step the crystalline material is subjected to drying.

**19 Claims, No Drawings**

US006906061B2

(12) **United States Patent**
**Uehata et al.**

(10) **Patent No.: US 6,906,061 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **PHARMACEUTICAL AGENT CONTAINING RHO KINASE INHIBITOR**

(75) Inventors: **Masayoshi Uehata**, Iruma (JP); **Takashi Ono**, Iruma (JP); **Hiroyuki Satoh**, Chikujo-gun (JP); **Keiji Yamagami**, Iruma (JP); **Toshio Kawahara**, Chikujo-gun (JP)

(73) Assignee: **Mitsubishi Pharma Corporation**, Osaka (JP)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/208,100**

(22) Filed: **Jul. 31, 2002**

(65) **Prior Publication Data**

US 2003/0134775 A1 Jul. 17, 2003

**Related U.S. Application Data**

(62) Division of application No. 09/791,648, filed on Feb. 26, 2001, now Pat. No. 6,451,825, which is a division of application No. 09/242,261, filed as application No. PCT/JP97/02793 on Aug. 8, 1997, now Pat. No. 6,218,410.

(30) **Foreign Application Priority Data**

Aug. 12, 1996 (JP) ..... 8-212409

(51) **Int. Cl.**[7] ..... **A61K 31/47**; C07D 401/12

(52) **U.S. Cl.** ..... **514/218**; 514/309; 540/575; 546/139

(58) **Field of Search** ..... 514/218, 309; 540/575; 546/139

(56) **References Cited**

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*Primary Examiner*—Zinna Northington Davis
(74) *Attorney, Agent, or Firm*—Wenderoth, Lind & Ponack, L.L.P.

(57) **ABSTRACT**

A Rho kinase inhibitor is provided as a novel pharmaceutical agent, particularly as a therapeutic agent of hypertension, a therapeutic agent of angina pectoris, a suppressive agent of cerebrovascular contraction, a therapeutic agent of asthma, a therapeutic agent of peripheral circulation disorder, a prophylactic agent of immature birth, a therapeutic agent of arteriosclerosis, an anti-cancer drug, an anti-inflammatory agent, an immunosuppressant, a therapeutic agent of autoimmune disease, an anti-AIDS drug, a contraceptive, a prophylactic agent of digestive tract infection, a therapeutic agent of osteoporosis, a therapeutic agent of retinopathy and a brain function improving drug. In addition, the Rho kinase inhibitor is provided as a reagent and a diagnostic.

**10 Claims, No Drawings**


(12) **United States Patent**
**Peschke et al.**

(10) **Patent No.: US 6,906,060 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **SUBSTITUTED HEXAHYDROPYRROLO[1,2-A]PYRAZINES, OCTAHYDROPYRIDO[1,2-A]-PYRAZINES AND DECAHYDROPYRAZINO [1,2-A]AZEPINES**

(75) Inventors: **Bernd Peschke**, Malov (DK); **Rolf Hohlweg**, Kvistgaard (DK)

(73) Assignee: **Novo Nordisk A/S**, Bagsvaerd (DK)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 149 days.

(21) Appl. No.: **10/453,106**

(22) Filed: **Jun. 3, 2003**

(65) **Prior Publication Data**

US 2004/0023916 A1 Feb. 5, 2004

**Related U.S. Application Data**

(60) Provisional application No. 60/387,047, filed on Jun. 7, 2002.

(30) **Foreign Application Priority Data**

Jun. 6, 2002 (DK) ..... 2002 00863

(51) **Int. Cl.**[7] ..... **A01N 43/00**; A01N 43/58; A61K 31/55; C07D 487/00; C07D 401/00

(52) **U.S. Cl.** ..... **514/214.02**; 514/249; 540/579; 544/238; 544/349

(58) **Field of Search** ..... 514/214.02, 249; 540/579; 544/238, 349

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*Primary Examiner*—Richard L. Raymond
*Assistant Examiner*—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Rosemarie R. Wilk-Orescan; Reza Green; Richard W. Bork

(57) **ABSTRACT**

Novel substituted hexahydropyrrolo[1,2-a]pyrazines, octahydropyrido[1,2-a]-pyrazines and decahydropyrazino [1,2-a]azepines, use of these compounds as pharmaceutical compositions, pharmaceutical compositions comprising the compounds, and a method of treatment employing these compounds and compositions. The compounds show a high and selective binding affinity to the histamine H3 receptor indicating histamine H3 receptor antagonistic, inverse agonistic or agonistic activity. As a result, the compounds are useful for the treatment of diseases and disorders related to the histamine H3 receptor.

**16 Claims, No Drawings**


(12) **United States Patent**
**Starke et al.**

(10) **Patent No.: US 6,906,058 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **1,5-BENZOTHIAZEPINES AND THEIR USE AS HYPOLIPIDAEMICS**

(75) Inventors: **Ingemar Starke**, Mölndal (SE); **Mickael Dahlström**, Mölndal (SE); **David Blomberg**, Mölndal (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/220,877**

(22) PCT Filed: **Mar. 5, 2001**

(86) PCT No.: **PCT/GB01/00909**

§ 371 (c)(1),
(2), (4) Date: **Sep. 6, 2002**

(87) PCT Pub. No.: **WO01/66533**

PCT Pub. Date: **Sep. 13, 2001**

(65) **Prior Publication Data**

US 2003/0166927 A1 Sep. 4, 2003

(30) **Foreign Application Priority Data**

Mar. 8, 2000 (SE) ..... 0000772

(51) **Int. Cl.**[7] ..... **C07D 281/10**; C07D 401/12; A61K 31/554; A61K 31/662; A61P 3/06

(52) **U.S. Cl.** ..... **514/211.1**; 540/552

(58) **Field of Search** ..... 540/552; 514/211.1

(56) **References Cited**

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*Primary Examiner*—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

The present invention relates to compounds of formula (I) wherein $R^1$ and $R^3$ are independently selected from $C_{1-6}$alkyl; one of $R^4$ and $R^5$ is a group of formula (IA): $R^2$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$ and $R^{11}$ and the other of $R^4$ and $R^5$ are as defined within, pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and there use as ileal bile acid transport (IBAT) inhibitors for the treatment of hypolipidaemia. Processes for their manufacture and pharmaceutical compositions containing them are also described.

**12 Claims, No Drawings**


(12) **United States Patent**
**Forman et al.**

(10) **Patent No.: US 6,906,057 B1**
(45) **Date of Patent: Jun. 14, 2005**

(54) **METHODS FOR MODULATING FXR RECEPTOR ACTIVITY**

(75) Inventors: **Barry M. Forman**, Newport Beach, CA (US); **Richard L. Beard**, Newport Beach, CA (US); **Roshantha A. Chandraratna**, Laguna Hills, CA (US)

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( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 422 days.

(21) Appl. No.: **09/590,447**

(22) Filed: **Jun. 9, 2000**

**Related U.S. Application Data**

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(51) **Int. Cl.**[7] ..... **A61K 31/551**; A61K 31/553; A61K 31/554; A61K 31/55

(52) **U.S. Cl.** ..... **514/211.08**; 514/211.15; 514/217.05; 514/218

(58) **Field of Search** ..... 514/211.08, 211.15, 514/217.05, 218

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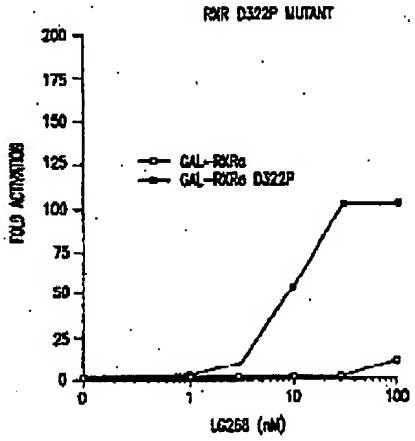
*Primary Examiner*—San-ming Hui
(74) *Attorney, Agent, or Firm*—Hamilton, Brook, Smith & Reynolds, P.C.

(57) **ABSTRACT**

Methods for modulating the activity of the mammalian FXR receptor. The methods include methods of treating a hyper- or hypocholesterolemic mammal comprising contacting the mammal with synthetic compounds having FXR receptor activity.

**30 Claims, 9 Drawing Sheets**




(12) **United States Patent**
**Thompson et al.**

(10) **Patent No.: US 6,906,056 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **CYCLOALKYL, LACTAM, LACTONE AND RELATED COMPOUNDS, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, AND METHODS FOR INHIBITING β-AMYLOID PEPTIDE RELEASE AND/OR ITS SYNTHESIS BY USE OF SUCH COMPOUNDS**

(75) Inventors: **Richard C. Thompson**, Frankfort, IN (US); **Stephen Wilkie**, Indianapolis, IN (US); **Douglas R. Stack**, Fishers, IN (US); **Eldon E. Vanmeter**, Greenwood, IN (US); **Qing Shi**, Carmel, IN (US); **Thomas C. Britton**, Carmel, IN (US); **James E. Audia**, Indianapolis, IN (US); **Jon K. Reel**, Carmel, IN (US); **Thomas E. Mabry**, Indianapolis, IN (US); **Bruce A. Dressman**, Indianapolis, IN (US); **Cynthia L. Cwi**, Indianapolis, IN (US); **Steven S. Henry**, New Palestine, IN (US); **Stacey L. McDaniel**, Martinsville, IN (US); **Russell D. Stucky**, Indianapolis, IN (US); **Warren J. Porter**, Indianapolis, IN (US)

(73) Assignees: **Elan Pharmaceuticals, Inc.**, South San Francisco, CA (US); **Eli Lilly & Company**, Indianapolis, IN (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/392,332**

(22) Filed: **Mar. 20, 2003**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

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(60) Provisional application No. 60/160,067, filed on Jun. 22, 1998.

(51) Int. Cl.[7] ..... **C07D 267/02**; C07D 487/00; C07D 223/12; A61K 31/55; A61P 25/28

(52) U.S. Cl. ..... **514/211.06**; 514/212.03; 514/212.04; 514/212.07; 540/491; 540/522; 540/523; 540/527

(58) Field of Search ..... 540/491, 522, 540/523, 527; 514/211.06, 212.04, 212.07, 212.03

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*Primary Examiner*—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Burns, Doane, Swecker & Mathis, LLP

(57) **ABSTRACT**

Disclosed are compounds which inhibit β-amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. Also disclosed are pharmaceutical compositions that include a compound which inhibits β-amyloid peptide release and/or its synthesis as well as methods for treating Alzheimer's disease both prophylactically and therapeutically with such pharmaceutical compositions.

**48 Claims, No Drawings**

US006906054B2

(12) **United States Patent**
**Buynak et al.**

(10) **Patent No.: US 6,906,054 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **COMPOSITIONS FOR INHIBITING BETA-LACTAMASE**

(75) Inventors: **John D. Buynak**, Dallas, TX (US); **A. Srinivasa Rao**, Waukegan, IL (US); **Greg C. Adam**, Dallas, TX (US); **Sirishkumar D. Nidamarthy**, Devon, PA (US); **Venkata Ramana Doppalapudi**, Dallas, TX (US)

(73) Assignee: **Research Corporation Technologies, Inc.**, Tucson, AZ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 12 days.

(21) Appl. No.: **10/143,636**

(22) Filed: **May 10, 2002**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

(62) Division of application No. 09/548,209, filed on Apr. 13, 2000, now Pat. No. 6,407,091.

(60) Provisional application No. 60/129,482, filed on Apr. 15, 1999.

(51) **Int. Cl.**[7] ..... **A61K 31/545**

(52) **U.S. Cl.** ..... **514/200**; 514/201; 514/202; 514/208; 514/209

(58) **Field of Search** ..... 514/200, 201, 514/202, 208, 209, 224.2

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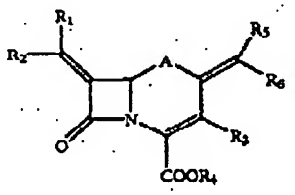
*Primary Examiner*—Phyllis G. Spivack
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg, Woessner & Kluth, P.A.

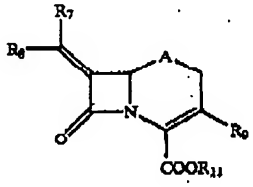
(57) **ABSTRACT**

The invention provides pharmaceutical compositions comprising compounds of formula I and IV:

I



IV



wherein $R_2$-$R_{11}$ and A have any of the values defined in the specification, and their pharmaceutically acceptable salts. The pharmaceutical compositions are useful for inhibiting β-lactamase enzymes, for enhancing the activity of β-lactam antibiotics, and for treating β-lactam resistant bacterial infections in a mammal.

**12 Claims, 4 Drawing Sheets**

US006906053B2

(12) **United States Patent**
**Sheppeck et al.**

(10) **Patent No.: US 6,906,053 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **HYDANTOINS AND RELATED HETEROCYCLES AS INHIBITORS OF MATRIX METALLOPROTEINASES AND/OR TNF-α CONVERTING ENZYME (TACE)**

(75) Inventors: **James E. Sheppeck**, Willington, DE (US); **Jingwu Duan**, Newark, DE (US); **Chu-Biao Xue**, Hockessin, DE (US); **Zelda Wasserman**, Wilmington, DE (US)

(73) Assignee: **Bristol-Myers Squibb Pharma Company**, Princeton, NJ (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/844,219**

(22) Filed: **May 12, 2004**

(65) **Prior Publication Data**

US 2004/0209874 A1 Oct. 21, 2004

**Related U.S. Application Data**

(62) Division of application No. 10/155,575, filed on May 23, 2002, now Pat. No. 6,890,915.
(60) Provisional application No. 60/293,571, filed on May 25, 2001.

(51) Int. Cl.[7] ..... **A61K 31/33**; C07D 487/00; C07D 233/00; C07D 221/00; C07D 215/00

(52) U.S. Cl. ..... **514/183**; 514/311; 514/385; 514/396; 514/399; 514/409; 514/412; 514/422; 514/425; 548/300.1; 548/300.7; 548/407; 548/408; 548/409; 546/112; 546/134; 546/16

(58) Field of Search ..... 514/183, 311, 514/385, 396, 399, 409, 412, 422, 425; 548/300.1, 407, 317.1, 409; 546/112, 134, 16

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| WO | | WO 01/23363 | 4/2001 |
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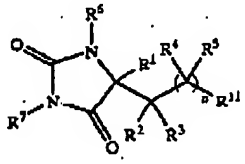
*Primary Examiner*—Richard L. Raymond
*Assistant Examiner*—Sudhaker B. Patel
(74) *Attorney, Agent, or Firm*—Jing G. Sun

(57) **ABSTRACT**

The present application describes novel hydantoin derivatives of formula (I):

(I)



or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{11}$, and n are defined in the present specification, which are useful as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase, or a combination thereof.

**24 Claims, No Drawings**

US006906051B2

(12) **United States Patent**
**Ruminiski et al.**

(10) **Patent No.: US 6,906,051 B2**
(45) **Date of Patent: Jun. 14, 2005**

(54) **LACTONE INTEGRIN ANTAGONISTS**

(75) Inventors: **Peter Ruminiski**, Ballwin, MO (US); **Thomas D. Penning**, Elmhurst, IL (US); **Lan Jiang**, Ballwin, MO (US); **Balekudru Devadas**, Chesterfield, MO (US); **Thomas Rogers**, Ballwin, MO (US); **Jennifer VanCamp**, Glencoe, MO (US); **Chester Yuan**, Souther Oaks, CA (US)

(73) Assignee: **Pharmacia Corporation**, St. Louis, MO (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/717,238**

(22) Filed: **Nov. 19, 2003**

(65) **Prior Publication Data**

US 2004/0116472 A1 Jun. 17, 2004

**Related U.S. Application Data**

(62) Division of application No. 09/963,926, filed on Sep. 26, 2001, now Pat. No. 6,720,327.

(60) Provisional application No. 60/241,633, filed on Oct. 19, 2000, and provisional application No. 60/235,617, filed on Sep. 27, 2000.

(51) **Int. Cl.**[7] ..... **A61K 31/33**; A61K 31/505; C07D 239/00; C07D 407/00; C07D 305/00

(52) **U.S. Cl.** ..... **514/183**; 514/514; 514/269; 514/256; 514/561; 514/482; 514/617; 514/473; 544/244; 544/297; 544/298; 544/322; 544/330; 544/335; 546/1; 549/263; 549/295; 549/321; 549/323

(58) **Field of Search** ..... 514/183, 269, 514/256, 561, 482, 617, 449, 473; 544/224, 297, 298, 322, 330, 335; 546/1; 549/263, 295, 321, 323

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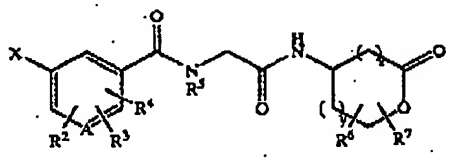
(57) **ABSTRACT**

The present invention relates to a class of compounds represented by the Formula I:

I



or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising compounds of the Formula I, and methods of selectively inhibiting or antagonizing the $\alpha_v\beta_3$ and/or the $\alpha_v\beta_5$ integrin.

**12 Claims, No Drawings**